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R&D SYSTEMS DYNAMICS IN
FEDERALLY REGULATED INDUSTRIES

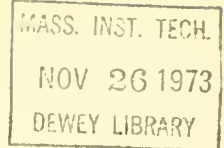
Jack W. Blanchard*

February 1973

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R&D SYSTEMS DYNAMICS IN
FEDERALLY REGULATED INDUSTRIES

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ABSTRACT

Historical examples of the deleterious effects of hazardous drugs were described. They were shown to lead to federal legislation controlling R&D in the pharmaceutical industry. Safety evaluation R&D extensively utilizes standardized toxicological methodology. Because of this, independent contract research laboratories have been able to provide professional services in standardized toxicology to the pharmaceutical industry. A case interview study employing prepared questionnaire forms was conducted. R&D managers in both the pharmaceutical companies and the independent contract research laboratories were interviewed in order to compare the management of standardized toxicological methodology as it applies to safety evaluation.

The results of standardized toxicological studies form the basis for determining the safety of drugs. These data, as summarized in petition form, are evaluated by the Food and Drug Administration in order to determine product compliance with federal law. A model of the interrelationship between the FDA, the pharmaceutical company, the independent contract research laboratory and the consumer, was presented as existing through information feedback systems based on safety evaluation R&D. This model was used to explain past R&D efforts associated with cause and effect relationships involving product safety associated with drugs.

The management of R&D involving product compliance is shown for the first time in this study. It serves to introduce a new factor of uncertainty associated with R&D, which is unique to industries whose products are regulated by federal law.

Congressional control in the food and drug industry began in 1906, with the enactment of the Federal Food and Drugs Act. It established federal precedence in regulating commerce of these materials among states and between the US and foreign countries. This Act was the first to establish federal authority in the protection of the public health from the illicit, harmful or injurious effects of foods and drugs.

In 1938, Congress repealed the Federal Food and Drugs Act when it proved inadequate in protecting public health. During 1937, a widespread outbreak of deaths in the US was found to be attributable to a purported drug, the Elixir of Sulfanilimide (1). The Act was then replaced by the Federal Food, Drug and Cosmetic Act of 1938. The effect of this new legislation was to outline specific federal controls in providing for the protection of the consumer from adulterated and misbranded foods, drugs, drug devices and cosmetics. In the case of new drugs, the Act specifically stated that no drug could be introduced into interstate commerce without the manufacturer submitting an application summarizing its R&D program which established the safety of that drug. In addition, information about its physical and chemical characteristics, manufacturing processes, labeling and a sample of the drug as well, was required by the provisions of the Act.

The Federal Food, Drug and Cosmetic Act was amended in subsequent years to provide for additional regulatory control over foods and color additives. These amendments instituted additional R&D requirements specifically addressed to these substances and their end-use. In 1961, however, another episode occurred involving drugs similar to that which resulted in the repeal of the old Federal Food and Drugs Act in 1938. In this case, the tragic events involving the use of thalidomide by expectant mothers resulted in a world-wide outbreak of phocomelia in the neonatal population (2). Instead of repeal, however, the Federal Food

Drug and Cosmetic Act was amended in 1962 in order to prevent the re-occurrence of the thalidomide episode involving other drugs. It directed that pharmaceutical companies, not only establish safety, but effectiveness and reliability of the drug as well. In addition, the amendment provided for the standardization of drug names, control on advertisements, factory inspection and effective control over state laws and finally, registration of drug manufacturing establishments and patent information of drugs. In essence, federal regulatory control was extended over the entire range of R&D and marketing activities of the drug industry.

The relationship between the regulatory agency and the pharmaceutical industry is, therefore, both legal and scientific. The legal justification for the Federal Food and Drugs Act of 1906, and its replacement, the Federal Food, Drug and Cosmetic Act of 1938, was Congressional authority to regulate interstate commerce. The failure to protect public health by simple legislation resulted in the detailed imposition of specific scientific requirements as a part of the law which had to be met by pharmaceutical companies prior to the commercialization of their products.

Regulatory control over drugs is maintained through the procedural process of petitioning. This interaction takes place between pharmaceutical companies and the Food and Drug Administration (FDA). Basically, the petition process is comprised of two separate sequences which correspond to the overall R&D program carried out by the pharmaceutical company in order to meet federal regulatory criteria. The first step summarizes the basic introductory R&D programs and is known as the investigational new drug application, or the IND. If the FDA approves and registers the IND petition, it allows interstate shipment of the experimental drug for more extensive animal studies and for clinical research using human volunteers. This is the second sequence of the R&D program in the petition process. At this time the candidate drug is not available for

for sale. Once the clinical research has been completed, the data are summarized in a new drug application petition, or the NDA. If the NDA is approved by the FDA, the drug is then allowed to be sold via interstate commerce. The procedural process is outlined below:

New drug development --- (leads to) --- Safety evaluation
in experimental animals --- (which results in) --- Investi-
gational new drug application to the FDA --- (which per-
mits) --- Clinical pharmacology (Phases I and II) --- (leads
to) --- Clinical trials (Phase III) --- (which results in) ---
New drug application to the FDA --- (which permits) ---
Commercialization of the drug.

New drug development and safety evaluation research in experi-
mental animals rely extensively on toxicology. The applicability of
toxicology to safety evaluation R&D has been substantiated over the
years by several significant publications. The most influential was
published by the technical staff of the FDA in 1959 (3). The methods
described in that publication had been in common use by Toxicologists
prior to 1959, however.

Toxicology is the scientific discipline devoted to the study of the
toxic characteristics of chemicals. The degree of toxicity is directly
related to the dose of the chemical given, the duration of its exposure,
the route of its administration and the species of animal in which the
chemical is investigated. Toxicology is the essence of safety evalua-
tion R&D, since the reciprocal of toxicity is safety.

A series of publications by Weil and the Food Protection Committee
of the National Academy of Sciences contributed information concerning
the effectiveness of toxicological methods in the safety evaluation of
chemicals (4, 5, 6). They dealt with substantially similar methods as
those published in 1959 by the FDA. Weil suggested that in feeding

studies using rats, some streamlining of long term studies (two years) could be made, based on predictions utilizing the results of short term (single exposure and three months) studies. The National Academy of Sciences found that on the basis of 10 years experience, short term and long term toxicological studies proved to be excellent indices in establishing the safety of drugs, economic poisons, food chemicals and cosmetics.

The most important impact of these publications was their standardization of toxicological methodology in safety evaluation R&D. Regardless of the chemical, whether drug, food additive, economic poison or cosmetic, the safe toxicological methods are employed in determining their safety. The extensive use of toxicology in determining the safety of chemicals was broadly incorporated into the Federal Food, Drug and Cosmetic Act to specifically provide data necessary for establishing the safety of chemicals the Act was responsible for. In the case of pharmaceutical companies, safety evaluation R&D programs are, therefore, based extensively on toxicological methodology.

Because of the widespread use of toxicological methodology in safety evaluation R&D, independent contract research laboratories have developed their own expertise in providing these services to manufacturers engaged in this type of R&D activity. They have been able to provide their services to manufacturers of many different chemicals. Their existence has provided manufacturers of drugs, food additives, economic poisons and cosmetics greater flexibility in the management of their safety evaluation R&D programs.

The financial commitment of pharmaceutical companies in toxicology is difficult to analyze. The extensiveness of the safety evaluation program depends on the candidate drug chemical and its intended use. In addition, expenditures assigned to the development of a particular drug are often not available, since the length of the R&D program

generally extends from 3 to 5 years prior to NDA approval by the FDA. Total R&D costs are sometimes available, however, for a drug or a category of drugs. This is not due to the intransigence of pharmaceutical companies, but simply because their accounting procedures are based on total R&D budgets, rather than costs of individual studies in various sequences in the R&D program. This is due to the fact that pharmaceutical companies maintain stable research facilities and personnel. In such cases, the number of individual studies performed and candidate drug chemicals investigated each year varies.

The latest complete financial data available for the drug industry come from the Pharmaceutical Manufacturers Association (PMA), their trade organization. They indicate that in 1969, on sales of \$6.225 billion, \$557 million were allocated to total R&D in the US (7). Further characterization shows that \$44.9 million were spent on in-house animal safety and toxicology. R&D expenditures assigned to contract research, that is research done in independent contract research laboratories, amounted to \$9.7 million. Since most of the contract research is in animal safety and toxicology, these expenditures represented an extensive financial commitment in safety evaluation R&D in 1969. Unfortunately, the PMA no longer includes these figures in their annual statistical summary of financial data for the pharmaceutical industry. They have estimated, however, that in 1971, there would be approximately \$7.592 billion in sales with \$681 million allocated to R&D (8).

It has been shown, therefore, that the basis of safety evaluation R&D is toxicological methodology, and it is extensively financed by the pharmaceutical industry. The basis of compliance with federal law is the establishment of safety. Because of its importance to those industries regulated by federal law, services in safety evaluation R&D, generally in the form of toxicological methodology, have formed the basis of supporting a growing number of independent contract research laboratories.

The Problem

The extensive financial commitment required to maintain complex safety evaluation R&D programs by pharmaceutical companies has resulted in their development of two separate research capabilities. These combine to offer them financial and technical advantages. Basically, in-house research facilities are most commonplace, and are relied on by many companies. However, depending on the company, the use of independent contract research laboratories as an adjunct, or replacement of in-house capabilities has become a necessity. The independent contract research laboratories have developed their expertise to simultaneously serve clients in other industries which also require safety evaluation R&D in order to commercialize their products.

The presence, therefore, of two separate research facilities, both involved in safety evaluation R&D, offers a unique opportunity for a case interview study in this field of R&D management. A close inspection of these research facilities reveals many similarities as well as some unique differences.

Similarities exist between both facilities in the scientific aspect of safety evaluation R&D. These are due to the standardized toxicological studies on which the concept of safety is based. Therefore, regardless of whether the studies are performed in the pharmaceutical company research laboratory, or in the independent contract research laboratory, they will require almost identical protocols.

Differences exist in the financial aspect of safety evaluation R&D between both facilities. The financial support of the pharmaceutical research laboratory is budgetary. That is, research is funded as a certain percent of the company income derived from product sales. The research facility is maintained regardless of the number of toxicological studies, or number of candidate drug chemicals. The financial support of the independent contract research laboratory, however, is based on the services it performs

for its clients. Its income is derived strictly from professional services either to the private sector, or to governmental agencies. The research facility maintained by the independent contract research laboratory is a direct function of the income it garners through the services it provides, and its size is directly related to this income.

Managerial techniques will be investigated as they exist within: A) different pharmaceutical research laboratories, B) different independent contract research laboratories, and C) between pharmaceutical company, and independent contract, research laboratories.

The applicability of these relationships relative to: A) past R&D performance in the pharmaceutical industry, and B) effect of federal regulatory controls involving R&D requirements on product safety with respect to drugs, will be discussed. In addition, the development of managerial skills unique to R&D management associated with federally regulated industries will be presented.

Materials and Methods

Directors of Safety Evaluation R&D of four pharmaceutical companies were interviewed. Pharmaceutical companies were selected which maintained annual worldwide sales in excess of \$100 million. Two operate a relatively small annual budget for contract research. These have been designated Company A and Company B. The remaining two operate a relatively large annual budget for contract research. These have been designated Company C and Company D.

Research Directors of four independent contract research laboratories were interviewed. The organizational structure of each laboratory was different. One was independently owned and still under the direction of the original owner and founder. It had been organized to provide services in preclinical toxicology to pharmaceutical companies in 1961, when these subsequently became an integral requirement of the new drug amendments to the Federal Food, Drug and Cosmetic Act in 1962. For purposes of

identification, it has been labelled Firm I. The remaining three firms are all subsidiaries of large organizations. The original entrepreneurs have left after taking their equity. Professional managers are presently administering these firms. Firm II is an international contract research laboratory in which there is no interaction between the management of the laboratory and the parent organization. Firm III is a national independent contract research laboratory, which is a subsidiary of an international professional service organization. There is no influence from the parent organization in the management of the research laboratory. Services offered by Firm III, however, do contribute to the total services of the parent organization. Firm IV is a national independent contract research laboratory which has recently been acquired and reorganized. It had been in operation during the development of more stringent safety requirements by the FDA in 1962, and had moved into the area of providing services in preclinical toxicology at that time. The management of Firm IV had previously been under stringent control by their former owners. Under new ownership, however, it is operating with a greater degree of autonomy.

All interviews were conducted personally. A standardized questionnaire form was used for the survey of the Directors of Safety Evaluation R&D at the pharmaceutical companies, and appears in Appendix I. Similarly, a standardized questionnaire form was used for the survey of the Directors of the independent contract research laboratories. Their questionnaire form appears in Appendix II.

Results

I. Pharmaceutical Companies:

A. Position, Experience and Educational Background (2)*

There were five professionals who participated in the case interview study. All were Directors of Safety Evaluation. Their responsibilities

* Corresponds to question number in the questionnaire form.

involved the management of laboratory animal toxicology and pathology. Their experience in safety evaluation R&D ranged from 10 to 20 years, and they had authored numerous publications. There was one MD, one DSc, one PhD, and two DVM's.

B. Organizational Design of the Research Facility (3)

In all cases, the Director exercised immediate control over the toxicology and pathology sections of the research facility. The design of the facility generally reflected the R&D requirements in support of the company products. Since all companies interviewed produce a wide variety of products, only personnel and facilities managed by the Directors were considered as influencing operating policy in safety evaluation R&D. In the case of Company C, their total complement was 40 staff members, of whom 7 were professionals. In the case of Company D, there were 40 personnel, of whom 4 were professionals.

C. Product Mix of the Company (4)

All companies produce ethical drugs. In addition, they market other products requiring standardized toxicological studies for safety evaluation research as required by either the Federal Food, Drug and Cosmetic Act, or the Federal Insecticide, Fungicide and Rodenticide Act.

D. Percent Utilization of the Research Facility (5)

There was a complete utilization of the research facility at all companies. Two of the companies had increased their staff to meet the demands of increased safety evaluation R&D (B, D). Methods development, in addition to safety evaluation R&D, was an active part of their research programs.

E. Resource Allocation and the Use of Outside Research (6, 7, 8)

All Directors utilize the services of independent contract research laboratories. The extent of their utilization depends on the operating policy of the company. In the case of the companies that use outside research facilities minimally (A, B), the Directors have convinced their

management that safety evaluation R&D done internally results in much greater control over the conduct of the research program, and consequently the data, although the overall costs are higher. For those companies that utilize independent contract research laboratories (C,D), top management has decided that for the moment they best serve the needs of the company. For example, Company C maintains limited research facilities and personnel. Any research exceeding their capacity is then contracted out. Company D, on the other hand, has incorporated contract research directly into the company's R&D program in a specific area, that of chronic feeding studies. Their reasoning in maintaining this policy is that forecasting the frequency of chronic feeding studies is difficult, and considering their fluctuation over the years, they have delegated this type of research to outside laboratories.

Given the general operating policy of the companies interviewed, research that is contracted out is done so at the discretion of the Directors, with the concurrence of their management. The considerations taken into account in electing to use outside research facilities are similar for all companies. They are:

1. To compensate for internal fluctuations in work-load,
2. To assist the company in meeting time requirement deadlines,
3. To provide technical expertise lacking within the company,
4. To provide additional work space for the company.

The selection process of independent contract research laboratories is similar for all companies. First and foremost, technical competence and personal knowledge of the professional in charge of the research to be contracted out is of utmost importance. Secondly, the cost of the research is also considered. Only one company listed proximity as a positive factor (C). Another had at one time considered this important in their selection process, but because of cost differentials among independent contract research laboratories, they could no longer afford to rely

on this factor (D).

Similar advantages in using independent contract research laboratories were voiced by all Directors. They provided resource flexibility in managing their own research programs, through the use of space, facilities and expertise not available internally at a cost that is attractive to them to get the job done.

F. Evaluation of Independent Contract Research Laboratories (9, 10, 11)

All Directors evaluated independent contract research laboratories favorably only if the laboratories had the expertise to do the job they advertised they could do. They would not use contract research laboratories in which they doubted their competence. Similarly, they had reservations about utilizing laboratories about which they knew very little, or had no experience themselves in the research which was to be contracted out.

Companies with a small contract research budget evaluated them on the basis of the competence of the scientists, rather than on the basis of the laboratory in which they worked. In terms of the laboratory, they regarded versatility in providing a wide variety of services as much more advantageous to them than merely their ability to do routine standardized toxicological research.

Companies which maintained a large contract research budget evaluated independent contract research laboratories on their ability to perform comparable studies, and subsequently selected them on the basis of scheduling and cost. Their selection process included provisions for recognizing their specialty within a particular field. In addition, they regarded the laboratory to perform as a functioning unit within their own research program, administrative compatibility, as quite important.

Continuation of the present policy toward the use of independent contract research laboratories will remain the same for one company from each category. The remainder are contemplating a change. The company operating on a small contract research budget is increasing their use of

the research laboratories of the foreign based affiliates within the company (B). As of the moment they are minimally used for teratology, reproduction and chronic feeding studies. If the present arrangement continues to work out well, they will consider their use as an alternative to the use of independent contract research laboratories. The remaining company with the large contract research budget is in the process of re-evaluating their present policy (D). This has been brought about due to their dissatisfaction in the maintenance of communication links with independent contract research laboratories during long term feeding studies. This has resulted in a lack of managerial control over the peripheral aspects of contract research.

G. Evaluation of Regulatory Agencies (12,13)

The FDA was evaluated on technical and administrative criteria. The FDA was judged as fair in technical areas. Overall operating guidelines for the FDA are unclear, since each division is managed somewhat autonomously. The lack of an impartial referee in resolving questionable scientific decisions was regarded as discouraging. In politically emotional climates the FDA tends not to do a good job. The demands for additional data by the FDA are sometimes not practical, or feasible, because of their unfamiliarity with the technical subtleties involved with safety evaluation R&D. The companies regard research guidelines as generally reasonable, however, they are reserving judgement on mutagenic guidelines until they become finalized.

Time restrictions imposed by the FDA which are initiated when requirements are published in the Federal Register are a real source of concern. This is especially true with regard to questions of format to be used in submitting data in support of compliance requests. The companies are hard pressed to cope with this type of requirement, since it becomes an administrative task, rather than an R&D requirement involving the establishment of the safety of the candidate drug chemical.

Company B regards the effect of FDA policy on long term research management as a function of the division within the FDA. The Cardio-pulmonary and Renal Drug Division was cited as not having approved any NDA's since 1966. Most of the companies have some NDA's which have not received approval after a period of up to 100 months. This, however, was not the general characteristic of the status of their NDA programs.

The evaluation of the Environmental Protection Agency (EPA), was primarily limited to those companies maintaining an R&D program in pesticides (B, C, D). Basically, the problems were attributed to organizational difficulties within the EPA in their managing compliance activities.

Company D has experienced difficulties while dealing with the EPA in which three different professionals have handled their petition. Within a six month period, a lack of coordination was quite apparent when they all made different technical decisions following their review of the same petition. Although the differences were not major, they have to be met before compliance will be granted. In the opinion of the company, this indicated a definite lack of overall operating policy in pesticides registration. The EPA, in their estimation, has yet to implement general operating guidelines for manufacturers to follow in pesticides registration procedures.

H. Effect of Regulatory Controls on R&D (14, 15, 16)

Research guidelines promulgated by the FDA have considerably increased R&D activity in the drug industry. In addition, FDA technical criteria are becoming more difficult with which to comply. They are asking for longer duration studies, increased sophistication in cross-over experiments in clinical studies investigating wash-out times for drugs. These studies, as well as bioavailability requirements, have added to the increase in total cost of R&D in new drug development.

The increasing demands of the FDA in R&D requirements will dras-

tically affect the present composition of the pharmaceutical industry. As of the moment, it takes on the average of 5 to 6 years to obtain NDA approval from the FDA. Very few small drug companies will be able to afford this type of delay and still rely on ethical drug sales as a major source of their income. As they diversify away from the manufacturing of ethical drugs, it will leave only the larger companies in the field.

The regulatory effects on R&D in safety evaluation from the National Institute for Occupational Safety and Health (NIOSH) have not yet been noticed by the companies interviewed. As to the effects of the National Center for Toxicological Research (NCTR), the pharmaceutical industry as represented by the companies interviewed is not able to evaluate whether or not it will have any impact. In order to meet the demands of regulatory controls from these, and other federal agencies, such as the Division of Biologics Standards, or the Department of Transportation, most of the companies have reorganized and expanded their corporate regulatory affairs departments. They serve to coordinate the activity of submitting safety evaluation data to the proper regulatory agency in order to meet the diversified demands of the various regulatory agencies.

I. Evaluation of the Pharmaceutical Manufacturers Association (17)

Technically, the PMA serves as an excellent medium in promoting the exchange of scientific information between members of the pharmaceutical industry through working committees of scientists. In judging the effectiveness of the PMA, however, difficulties arise when it comes to the issuance of statements of methodology resulting from these working committees. Prior to their release, they are reviewed by non-technical committees and other corporate committees within the PMA. The complex review process results in either extensive delay, or failure to issue the statement. This is generally why the PMA is ineffective as the representational spokesman for the drug industry.

J. R&D Trends in the Pharmaceutical Industry (18, 19)

FDA directives influence R&D management through their requirements for sophisticated research in safety evaluation studies. Bio-availability, the effect of colors on the safety of drug formulations, and the question of the safety of saccharin have resulted in increasing the amount of clinical research. There is an overall increase in the degree of regulatory control that is being exerted on the pharmaceutical industry in terms of safety evaluation research required for their products.

The trend in R&D management is to increase flexibility of their research capabilities. Some companies are evaluating the incorporation of R&D laboratories of their foreign based affiliates. Others will continue to rely on independent contract research laboratories to provide research services not routinely done internally. Their use for long term studies depends on the company and their satisfaction with the administrative arrangements involved with their management.

II. Independent Contract Research Laboratories:

A. Position, Experience and Educational Background (2, 3)

There were five individuals that participated in the case interview study. All had PhD degrees. All of them were, or had been, closely associated with the management of safety evaluation R&D. Three had an average of 9 years experience in independent contract research laboratories. Two had an average of 3 years experience, following 12 years of prior experience in the pharmaceutical industry. All of the professionals were members of scientific organizations, and had authored numerous technical publications.

B. Organizational Design of the Firm (4)

Firm I is owned and managed by its founder. It employs approximately 100 personnel, of whom 7 hold doctoral degrees. It is comprised of three operating divisions. Firm II underwent reorganization following acquisition and employs approximately 80 personnel, of whom 7 hold doctoral degrees. It is comprised of four operating divisions. Firm III

did not undergo reorganization following acquisition by a larger company. It retained a staff of 30 personnel, of whom 4 are doctoral level professionals, all of whom are engaged in biological research. It is comprised of four operating divisions. Firm IV underwent extensive reorganization following acquisition, and currently employs approximately 350 personnel, with a professional staff of 33 holding doctoral level degrees. It is comprised of 5 operating divisions.

C. Products Evaluated and Distribution of Services (5, 6, 7)

Each of the firms interviewed has the capacity to test any of the products regulated by the Federal Food, Drug and Cosmetic Act. The distribution of their services, therefore, is dependent on their success in garnering research contracts in a particular field. Their services primarily involve the use of laboratory animals. Two of the firms interviewed, for example, are substantially involved in providing services in preclinical pharmacology (I, IV). Screening studies, however, represent a minor source of income. Analytical and clinical chemistry, as well as microbiology studies are not consistent producers of income among the firms, however, Firm II derives substantial income in microbiology. Domestic animal studies do not form a major portion of the services offered by the firms interviewed. All firms are attempting to increase the volume of their services while expanding into new areas of expertise. They provide services to clients in safety evaluation R&D relative to federal laws other than the Federal Food, Drug and Cosmetic Act, such as the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), and the Federal Hazardous Substances Act (FHSA). One firm has begun to service client accounts in R&D management (III).

D. Resource Allocation and Decision Making in Maintaining Service Viability (8, 9, 10)

Resources are committed to establish services to meet anticipated needs of the client in satisfying regulatory criteria. Internal financial

requirements are greatest for direct labor costs. These are offset by allocating income from government contracts for salaries, while allocating income from private sector accounts to other categories, such as the introduction of new services. All firms are expanding their services in an attempt to offset fluctuations in the business of contract research. New services are initiated and project proposals issued only if the expertise is available within the firm. All firms utilize overtime of non-salaried employees, part-time help and subcontracting of pathology work in order to handle excess work-load relative to the capacity of the firm.

E. Client Contact and its Relationship to Performance of the Firm (11, 12, 13, 14, 15, 16, 17, 18)

Performance is defined as the amount of sales derived from services in response to client contact. All services provided by these firms in toxicological methodology to the private sector clients are of specific duration, ranging from 2 weeks up to 2 years. When dealing with the federal government, however, research services tend to be open-ended. Only professional staff members are involved in client contact. Personal contact is preferred by all firms, and is usually done on a one-to-one basis with private sector clients. Special units are assigned to garner government contracts and generally are not involved with private sector client contact. The ratio of private sector to government contract accounts is dependent on the operating policy of the independent contract research laboratory. Firms I and III do not have any government contract accounts. Firms II and IV do have government contracts. Most firms allocate income from government contract accounts toward operating expenses. Income from private sector accounts is determined by what the market will bear. The two sources of income are utilized by the independent contract research laboratory in order to maintain its business viability. By far the most important to the firm is income derived from private sector accounts.

The incidence of client contact is high prior to the initiation of any study. Once the study is initiated, however, it is dependent on its duration. The longer the study, the more frequent the contact. Private sector clients from large companies are generally technically oriented whereas, clients from smaller companies are administratively oriented. Client contact is generally not shifted from one professional to another during the study. Without client contact, there are no sales or services. Its indication of performance of the firm is absolute. The success of the client contact resulting in sales is directly dependent on the professional competence of the individual representing the firm. A lack of client contact was directly responsible for decreased accounts of Firm IV prior to its acquisition. Since income of the firm is derived from sales of its services, the profitability of all firms interviewed indicates that they are all positive performers.

F. Evaluation of Technical, Administrative and Financial Performance (19,20, 21, 22, 23)

All firms interviewed used similar evaluation procedures. Technical performance was measured internally by management of the scientific aspects of the study, and externally by the evaluation of the report by the client. Generally the professional staff member responsible for the study, on the basis of his contact with the client, was in charge of the technical survey. In cases where studies are repetitious, technical surveys are no longer done. Administrative performance was measured internally by the report preparation process, in addition to the cost of the study; and externally by client satisfaction associated with the issuance of the final report. Weekly records of the progress of in-house studies at various stages of completion are kept by two of the firms (II, IV). Weekly surveys are not kept at Firm I for repetitive studies, but are kept for new studies. Costs are assigned to studies on the basis of the professional and administrative time charged to them. In addition, material costs are additional charges.

Management committee meetings are held periodically. Two of the firms have experienced managerial difficulties due to the separation of the management from the laboratory. Firm II has encountered difficulties in the internal management of the firm because of the physical separation of the laboratory management. Although the Directors of each laboratory meet quarterly, communication between them is difficult during the remainder of the year. Without the closeness of management caused by the international structure of the firm, coordination of policy on technical, administrative and financial matters is difficult to maintain. Management skilled in safety evaluation R&D and familiar with federal regulatory criteria is absolutely essential if the firms are to achieve positive financial performance.

Prior to its acquisition, the former management of Firm IV was unfamiliar with the research requirements of the Federal Food, Drug and Cosmetic Act. In addition, they were physically separated from the laboratory. The result was that they mismanaged the firm badly enough such that it resulted in a negative financial performance during its entire period of control. Conversely, since acquisition, with management at the laboratory and professionals skilled in safety evaluation R&D, Firm IV has maintained a positive financial performance.

Firm I has been profitable over the past 5 years. Firm II has assumed a profitable posture. Firm III has always been profitable. Firm IV, since acquisition, has been operating profitably.

Internally, all firms used the profit and loss statement as the overall measure of the firm's technical, administrative and financial performance. Externally, comparisons with each other on competitive bidding was used to evaluate their technical, administrative and financial performance.

G. Evaluation of Client's and Competitor's Research Facilities (24, 25)

In the pharmaceutical industry, there is a negative correlation between sales and R&D competence, and a positive correlation between

good company management and R&D management according to Firm I. The experience of Firm II has been that the larger the company, the better staffed and equipped its research laboratory.

Evaluation of the competitor's research facilities is based primarily on the results of competitive bidding. Client feedback on criticism of competitors capabilities was used as a basis of evaluating the competitors of Firm II. It was the opinion of Firm III that all of their competitors were good businessmen, and given the fact that all were competent professionals, their ability to maintain client contact resulted the success of the firm.

H. Evaluation of Regulatory Agencies (26)

The FDA was judged as having a realistic operating policy by Firm III. On the other hand, Firm IV expressed reservations about the operating policy of FDA, and rated it as unrealistic, along with its unwillingness to make decisions and characterized the FDA as ineffective in its supervision of personnel. Firm III had the opposite opinion of the EPA, however, than it expressed for the FDA. They had experienced considerable difficulty in pesticide registration when representing their clients. This manifested itself in extensive delay by the EPA in meeting its own guidelines for time limits in responding to petition registration applicants. In addition, EPA had lost R&D data submitted to them by Firm III on behalf of their clients. Inconsistent rulings on the part of different personnel at the EPA had also been experienced by Firm III. In the opinion of Firm IV, personnel in pesticide registration at the EPA are inexperienced, and this results in a lack of decision-making. Both firms agreed that there is ineffective supervision of personnel and that effective management is non-existent in pesticides registration.

I. Factors in the Success of the Firm (27)

The primary factors in the success of independent contract research laboratories were similar for each firm interviewed. Competence of

the professional staff was paramount. Facilities and full service capabilities in R&D were also mentioned. Strong marketing with its concomitant client contact were also cited. Proximity to the clients was cited by two of the firms interviewed (I, II).

J. Business Trends in Contract Research (28, 29)

Preclinical as well as clinical research on an individual candidate drug chemical could be done entirely within the independent contract research laboratory according to Firm I. In the opinion of Firm IV, however, independent contract research laboratories could replace only toxicological research for pharmaceutical companies, while for agricultural chemical companies, they could replace their toxicological, pharmacological, quality control, metabolism and chemical stability research capabilities.

Business trends in the field of independent contract research are directly related to government regulatory criteria. Without them, there would be no business. Forecasting trends of impending regulatory criteria in terms of providing the appropriate R&D services must be accompanied by the ability of the firm to commit resources in order to meet the expected demand. There appears to be a conscious effort on the part of the firms interviewed toward offering a broad spectrum of services, rather than relying on a particular specialization. In the opinion of Firm II, the number of firms in existence today will diminish, either by attrition or consolidation. Also, the number of federal contracts will begin to increase, in contrast to past years.

Discussion

Regardless of whether they worked for pharmaceutical companies or independent contract research laboratories, the professionals interviewed were highly educated and had extensive experience in safety evaluation R&D. In addition, they were active in their individual field of expertise, as evidenced by their publication records.

Organizational differences between pharmaceutical, and independent contract research laboratories reflected their business operating policies. The research effort of the pharmaceutical company culminates in both the IND and the NDA. The function of the Director of Safety Evaluation is the integration of the data derived from the research under his direction into the petition required for FDA approval. Since the research programs undertaken by the pharmaceutical companies in safety evaluation R&D involve the use of standardized toxicological studies, independent contract research laboratories have developed the expertise to perform these services for a fee. Whether or not they are subsidiaries, or independently owned, their organizational design reflected how they best accomplished contract research in toxicology.

The personnel of pharmaceutical companies maintaining a large contract research budget and independent contract research laboratories showed some similarity in the percentage of professional level individuals in the total number of R&D personnel. This ranged between 7 and 13%, with an average of 9.5%. In the case of pharmaceutical companies, this applied to their toxicology and pathology departments only. In the case of independent contract research laboratories, however, this applied to their total work force. These data are based on a small sample, and should not be extrapolated to the industry as a whole. Pharmaceutical companies with a small contract research budget maintained a large pool of R&D personnel in order to accomplish all of their research objectives.

The business relationship between pharmaceutical companies and independent contract research laboratories is based on products which require safety evaluation R&D, as regulated by the Federal Food, Drug and Cosmetic Act. The relationship between the independent contract research laboratories and large pharmaceutical companies is maintained between professionals both competent in toxicology and safety evaluation R&D. Smaller pharmaceutical companies have professionals representing

their scientific staff which tend to be less familiar with the technical aspects of safety evaluation R&D, and more administratively oriented. They are generally much more concerned with the financial aspects of contract research.

In general, independent contract research laboratories receive overflow research in excess of the research capacity of large companies. Medium companies may or may not have the technical expertise, and they're usually looking at the financial area critically in which contract research offers them expertise they may not be able to incorporate internally into their own facilities. Small company clients don't have the technical expertise and usually look at the financial areas very critically. For small companies, contract research offers them what they themselves don't have, a research laboratory.

The independent contract research laboratory provides professional services in toxicological methodology. Its income is derived on the basis of either individual studies, or research projects. The majority of toxicological studies are of short term duration, usually 6 months or less, while a few are intermediate and long term in length, ranging from 18 months to two years. Generally, private sector clients utilize their services in this manner. Research projects, on the other hand, are combinations of short, intermediate and long term toxicological studies, usually performed for government contracts. Regardless of the source of income, independent contract research laboratories maintain operating objectives which are directly related to the duration of the studies, or the projects they perform, since these are their only source of income.

Pharmaceutical companies maintain an R&D capacity consistent with their business operating policy, as reflected in the two categories outlined in this study. They are specialists in ethical drug R&D, and through various combinations of their internal research capacity and the use of independent contract research, they are able to maintain their R&D programs

in order to meet federal regulatory criteria pertaining to their products. Independent contract research laboratories have the capacity to test any product manufactured by the pharmaceutical industry. Some have strengths in special areas of research. In addition, they have the capability of servicing other industries whose products are regulated by other federal laws which also require safety evaluation R&D programs.

Pharmaceutical companies interviewed in this study contract out research studies that exceed the capacity of their research facility. Their use of independent contract research laboratories is generally in response to the fluctuation in their work load or to time requirements. Similarly, independent contract research laboratories subcontract out research in order to compensate for fluctuations in work load, or to meet time requirements. There are differences between the two relationships in that pharmaceutical companies contract out research in order to: 1) provide expertise lacking within the company, and 2) provide additional work space within the research facility. Independent contract research laboratories, on the other hand, generally contract out only pathology work which exceeds the work load capacity of their facilities.

Evaluation of independent contract research laboratories by pharmaceutical companies revealed subtle differences which corresponded to the extent of their use by the company. Companies which maintained either a small or a large budget for contract research regarded personal knowledge of the individual scientist and technical versatility of the independent contract research laboratory as important factors. In addition, however, those companies which maintained a large budget for contract research, regarded technical expertise on comparable studies by different independent contract research laboratories, knowledge of the specialty of various firms and their ability to accomodate administratively, as high priority factors.

In the evaluation of pharmaceutical companies by the independent con-

tract research laboratories, there was no indication of a positive correlation between company sales and competent research. They did note, however, that there was a positive correlation between good company management and competent research management.

Internal review of their performance by the independent contract research laboratory was based on maintaining close control over the technical and administrative variables by the firm. Its overall success, however, was based on financial performance. Relative to private sector accounts, this was intimately associated with client contact and its close relationship to client satisfaction. All firms recognized and reacted to the importance of personal client contact and client feedback in its relationship to profitability with regard to private sector client accounts. Government contracts tended to be impersonal and not as dependent on client contact for renewal.

The evaluation of the FDA by pharmaceutical companies and independent contract research laboratories reflected the degree of influence exerted by the Agency upon each. The pharmaceutical companies evaluated the FDA at many different levels of its operation, reflecting the close relationship between the Agency and the companies. The FDA was judged fair in technical areas, although the lack of overall control on technical judgments within the FDA resulted in unclear operating objectives. On occasion, the FDA had requested data which tended to be either unreasonable to the objectives of the petition, or not technically practical. This was thought to be due either to a lack of sufficient familiarity with the research procedures, or the imposition of politically emotional constraints upon the FDA. The separation of administrative requests upon the pharmaceutical companies from technical controls, was difficult to deal with, especially with reference to time limitations and data format presentation. There was a split in the evaluation of the FDA by the independent contract research laboratories, between what was stated as "realistic" and "unrealistic

operating policies. Their evaluation, however, was confined only to this descriptive term, and was not specific. Agreement existed between the pharmaceutical companies and the independent contract research laboratories, however, on the indecisiveness of the FDA. Particular note was made of the total absence of NDA approvals by the Cardiopulmonary and Renal Drug Division of the FDA since 1966.

There was general agreement between the pharmaceutical companies and the independent contract research laboratories concerning the existence of ineffective management in pesticides registration at the EPA. The organizational difficulties attributed to the EPA have resulted in an absence of an overall operating policy in this area. Inconsistency in technical judgments by different personnel were experienced by both the pharmaceutical companies and the independent contract research laboratories.

As regulatory controls over R&D by the FDA have increased, so has the cost. The demand for longer duration studies, greater sophistication in research methods, have forced the pharmaceutical industry to increase their research capability, which has increased their operating costs. The larger companies have been able to meet the regulatory criteria of the FDA much more easily than the smaller companies. It was the opinion of the interviewees representing the pharmaceutical companies that increasing regulatory requirements in the industry would force smaller companies to diversify away from ethical drug manufacture. Those companies maintaining their commitment to ethical drug production are also affected by other federal laws, and consequently other regulatory agencies. In order to meet the diversified regulatory requirements, pharmaceutical companies have, in general, begun to reorganize and expand their corporate regulatory affairs departments. None of the independent contract research laboratories regard knowledge of regulatory requirements as a saleable service, but rather an entrée into obtaining client accounts in toxicology.

The success of independent contract research laboratories is directly related to their ability to meet the increasing demands for R&D services of the pharmaceutical industry resulting from the imposition of federal regulatory controls. Their technical competence and professional expertise, coupled with their research facilities, strong marketing through client contact, and proximity to the pharmaceutical companies, have all been important factors in their success.

The degree of profit made by the independent contract research laboratory is inversely proportional to the time span associated with their operating objectives, and directly proportional to the risk. Objectives based on a per study basis; that is, dealing with private sector clients, bring the greater margin of profit. Objectives based on research projects; that is, dealing with government contracts, bring a lower margin of profit. Income derived from toxicological studies requires a constant marketing effort which is highly dependent on personal contact. Once the studies are completed, income ceases, which then initiates the marketing effort. Income derived from research projects requires a different marketing approach. Projects last for a longer period of time, generally on an annual basis. Garnering government contracts does not require a high degree of personal contact, but rather involves written proposals which are submitted to the appropriate government granting agency for approval and funding.

The increasing degree of federal regulatory R&D requirements imposes a greater response in R&D activities by the pharmaceutical industry, subsequently generating more business for the independent contract research laboratories. As a result, there appears to be a trend toward a greater flexibility of the research facilities in both. Pharmaceutical companies have expanded their use of foreign based research affiliates. Independent contract research laboratories have expanded their capabilities in the drug area to include clinical, as well as preclinical research. Without the

presence of federal regulatory requirements involving product safety, there would not be as large an effort in R&D by the pharmaceutical industry, and similarly, there would be fewer independent contract research laboratories in business.

Summary and Conclusions

The main product of the pharmaceutical research laboratory is the petition, which summarizes for the company all the available research data on a candidate drug chemical. It is used to provide evidence of safety and efficacy to the FDA in order to obtain compliance with the appropriate federal law. This subsequently leads to commercialization of the product, thus generating sales revenues for the company. The income of the research laboratory, therefore, is based on product sales, from which their budget is derived. Its objectives are long term in that they are oriented toward product compliance research. This includes not only managing the R&D phase, over which it has direct control, but also managing the compliance phase.

The interrelationship between the pharmaceutical research laboratory and the independent contract research laboratory is quite dynamic. Not only is this due to the fact that the interaction is based on toxicological studies of specific duration, but also because there are a number of independent contract research laboratories that are competing with each other to provide similar services to the pharmaceutical industry whose demands are directly influenced by the FDA.

Long term operating objectives involve the development of expertise in mastering new toxicological methods. These are directly related to research guidelines issued by the FDA which become incorporated into the product safety R&D process. Independent contract research laboratories make decisions in committing resources such that the expertise is developed at just the right moment in order to maximize the advantage over their competitors. Similarly, pharmaceutical research labora-

tories commit resources in developing new toxicological methods for compliance purposes in safety evaluation R&D. They may rely to some extent, however, on independent contract research laboratories to provide them with the expertise in this area, either initially or permanently, depending on the operating policy of the pharmaceutical company.

Methods development by independent contract research laboratories in anticipation of new federal regulatory criteria imposed on the pharmaceutical industry may be described as either low, or high risk operations internally. It depends on the professional skills, equipment and capital required. If these factors are already available, then it is a low risk operation. If the professional skills, equipment and capital must be obtained, it represents a high risk operation. Regardless of the resources required, however, it is a high risk venture externally, since it must be developed and marketed at precisely the right moment. Too early, and there will be a lack of demand, too late and the competition will have already become too great to regain the investment costs within an acceptable period of time.

Safety evaluation R&D in the federally regulated pharmaceutical industry as described in this report operates as a network of information feedback systems. There exists three distinct information feedback systems operating in the research model selected for this case interview study. These illustrate the influence of extra-organizational factors on R&D management. Basically, the desired goal of the independent contract research laboratory is to provide research services in toxicological methodology for a profit. The goal of the pharmaceutical company is to achieve product compliance through toxicological methodology and clinical studies, subsequently leading to commercialization and sales income. The goal of the FDA is consumer protection from the deleterious effects of products under its jurisdiction. All of these goals exist in a "steady state system".

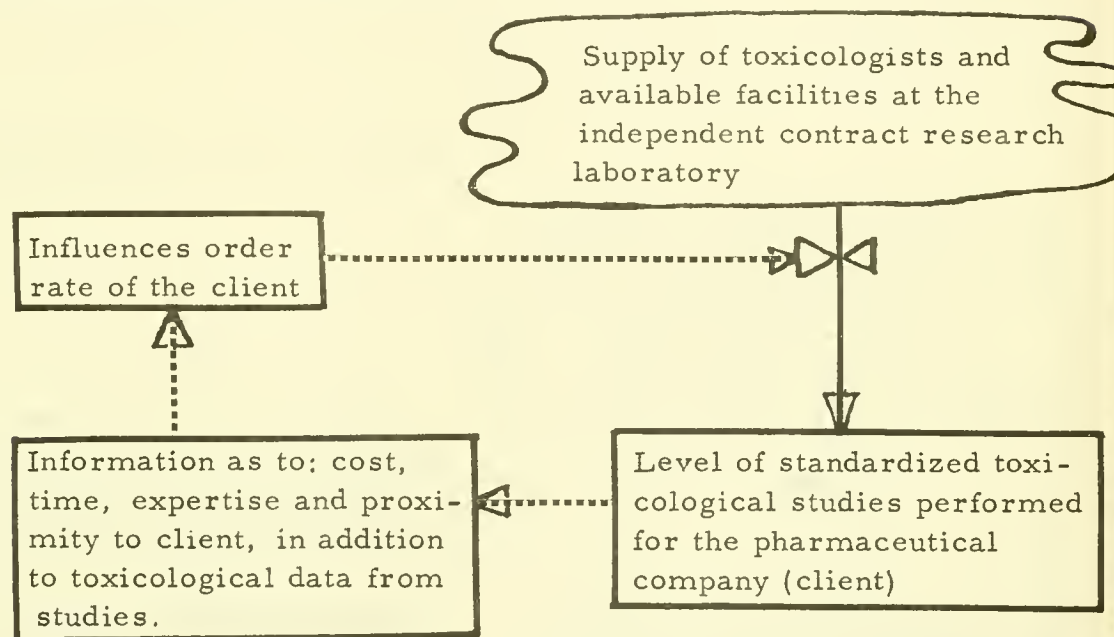
Information feedback systems applied to management have been previously reported by Forrester (8, 9). Its application to R&D management was first described by Roberts (10). Information feedback systems in R&D interrelate the existence of multiple factors affecting research goals relative to time. It allows for a greater flexibility of management within the organization for more effective decision making activities. This study is the first which describes these systems applied to R&D management in a federally regulated industry operating at the extraorganizational level.

The first two levels of information feedback systems exist at the company-contract research laboratory level, and the company-regulatory agency level. They are operative in the petition preparation and product registration processes respectively. They are both first order negative feedback loop mechanisms. The third level of information feedback system exists between the pharmaceutical company and the combination of both the consumer and regulatory agency. This system operates in both a first order and second order negative feedback loop. It is activated only following the failure of the first order negative feedback loops associated with the first two levels of information feedback systems, which are intended to establish the safety and efficacy of the product prior to commercialization. In essence, the third level operates as a back-up system.

The driving force of the first level of information feedback system, that existing between the pharmaceutical research laboratory and the independent contract research laboratory, is the dynamic interaction involving toxicological methodology on a per-study basis. The independent contract research laboratory has a supply of toxicologists, and the facilities necessary to provide services in toxicology. It provides these services, as reported in this study, on the basis of: cost, ability to initiate the study quickly (time), expertise, and in some cases proximity

to the client. The pharmaceutical research laboratory selects the contract research laboratory on the basis of these factors. The diagram that follows outlines the first order negative feedback loop characteristics of this interrelationship, which is called the Studies System Dynamics Model. Since these standardized toxicological studies are of specific duration, and the fact that the independent contract research laboratory serves many clients simultaneously, the Studies System Dynamics Model operates at a rapid rate.

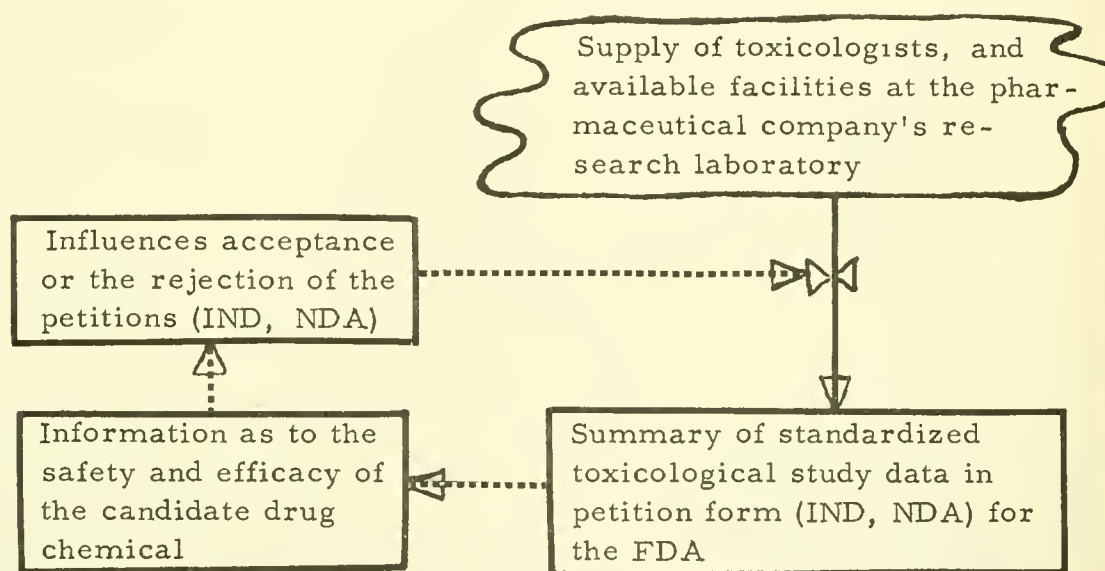
Studies System Dynamics Model



The driving force of the second level of information feedback system, that existing between the pharmaceutical company and the FDA, is the company's R&D objectives in obtaining compliance with federal law for their candidate drug chemicals. The pharmaceutical company has a supply of toxicologists, as well as the facilities required to carry out the necessary research program. The Director of Safety Evaluation is responsible for defining the toxicological characteristics, the degree of safety, associated with their candidate drug chemical. The data generated on preliminary, or screening studies are used to design a sequence of more com-

plex toxicological studies. The end product of the research program is a detailed report, the IND petition, summarizing the safety of the candidate drug chemical, and the NDA petition, summarizing its efficacy. The pharmaceutical company requests compliance with federal law through the jurisdiction of the FDA on the basis of the petition. The diagram illustrated below outlines the first order negative feedback loop characteristic of this interrelationship, which is called the Petition System Dynamics Model. Because of the extensiveness of the research program, and the time requirements of the review process of the petitions employed by the FDA, the Petition System Dynamics Model does not operate at as rapid a rate as the Studies System Dynamics Model.

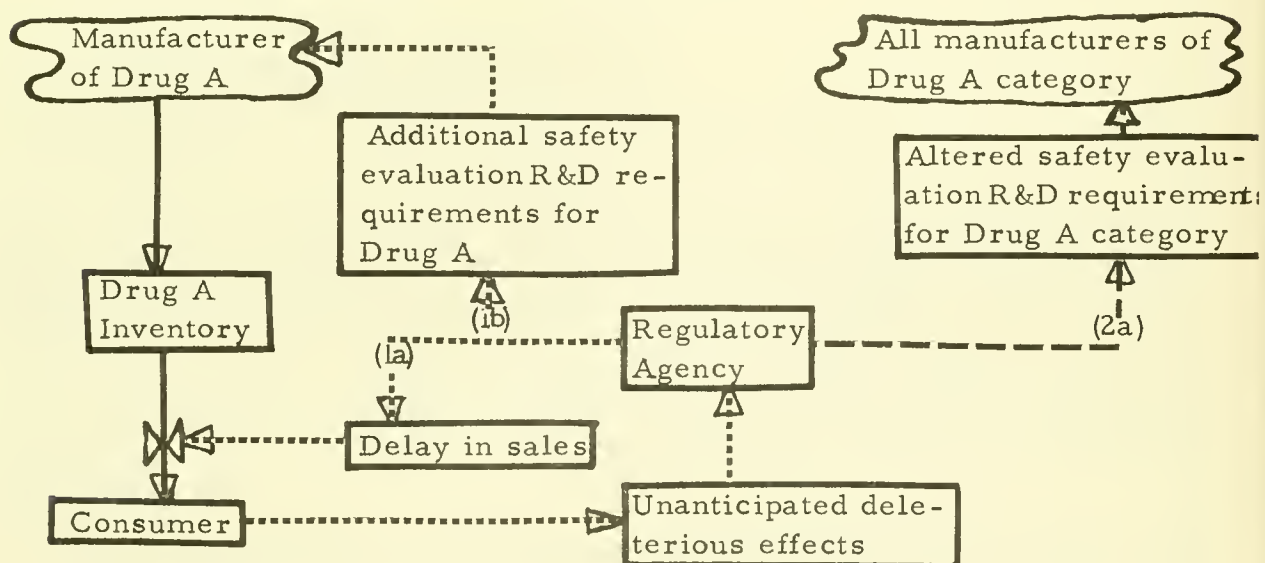
Petition System Dynamics Model



The occurrence of either unanticipated deleterious effects of the drug on the consumer, or subsequent research data indicating potential harmful effects of the drug following its commercialization, is the driving force of the third level of information feedback system. It operates between the pharmaceutical company, the consumer and the FDA. If either one or both of these factors occur, first and second order negative

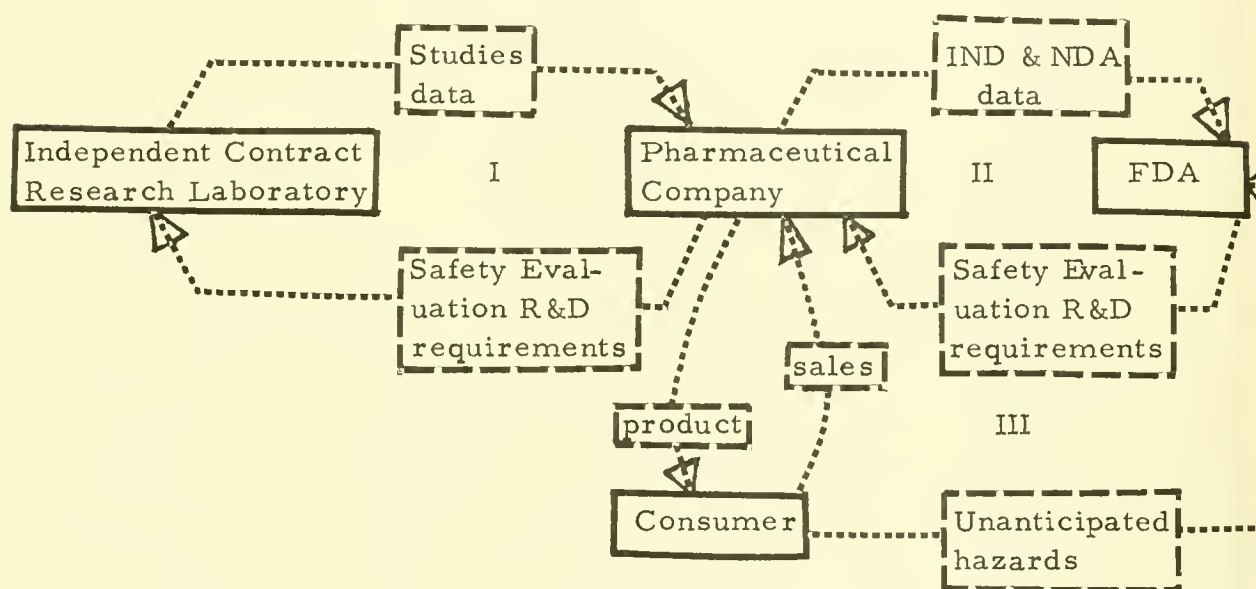
feedback loops are activated. They operate in two sequences. The first initially affects the sale of the drug itself, while the second affects the commercialization of all subsequent drugs, irrespective of the manufacturer. The diagram illustrated below includes characteristics of the interrelationships between the pharmaceutical company, the consumer and the FDA. It is called the Consumer Protection System Dynamics Model. Its complexity, however, requires an explanation. The first sequence involves the delay of drug sales (1a), and operates at a rapid rate. It also involves the requirement of additional R&D data to definitively establish drug safety (1a). The first sequence, parts 1a and 1b, operates at generally the same rate as the Petition System Dynamics Model. The second sequence (2a), represents the altered R&D requirements for all products in the original drug category, and subsequently all drugs under the jurisdiction of the FDA. It operates at a much slower rate than that seen in the Petition System Dynamics Model. It includes the development of new toxicological methodology, which results in the issuance of new research guidelines by the FDA. These are then subsequently incorporated into safety evaluation R&D requirements for the registration of all new candidate drug chemicals.

Consumer Protection System Dynamics Model



These information feedback systems serve to illustrate that safety evaluation R&D in the pharmaceutical industry exists in a dynamic steady state. It operates between the independent contract research laboratory, the pharmaceutical company, the Food and Drug Administration and the consumer. On the basis of the data presented in this report, the diagram illustrated below simultaneously summarizes these interactions.

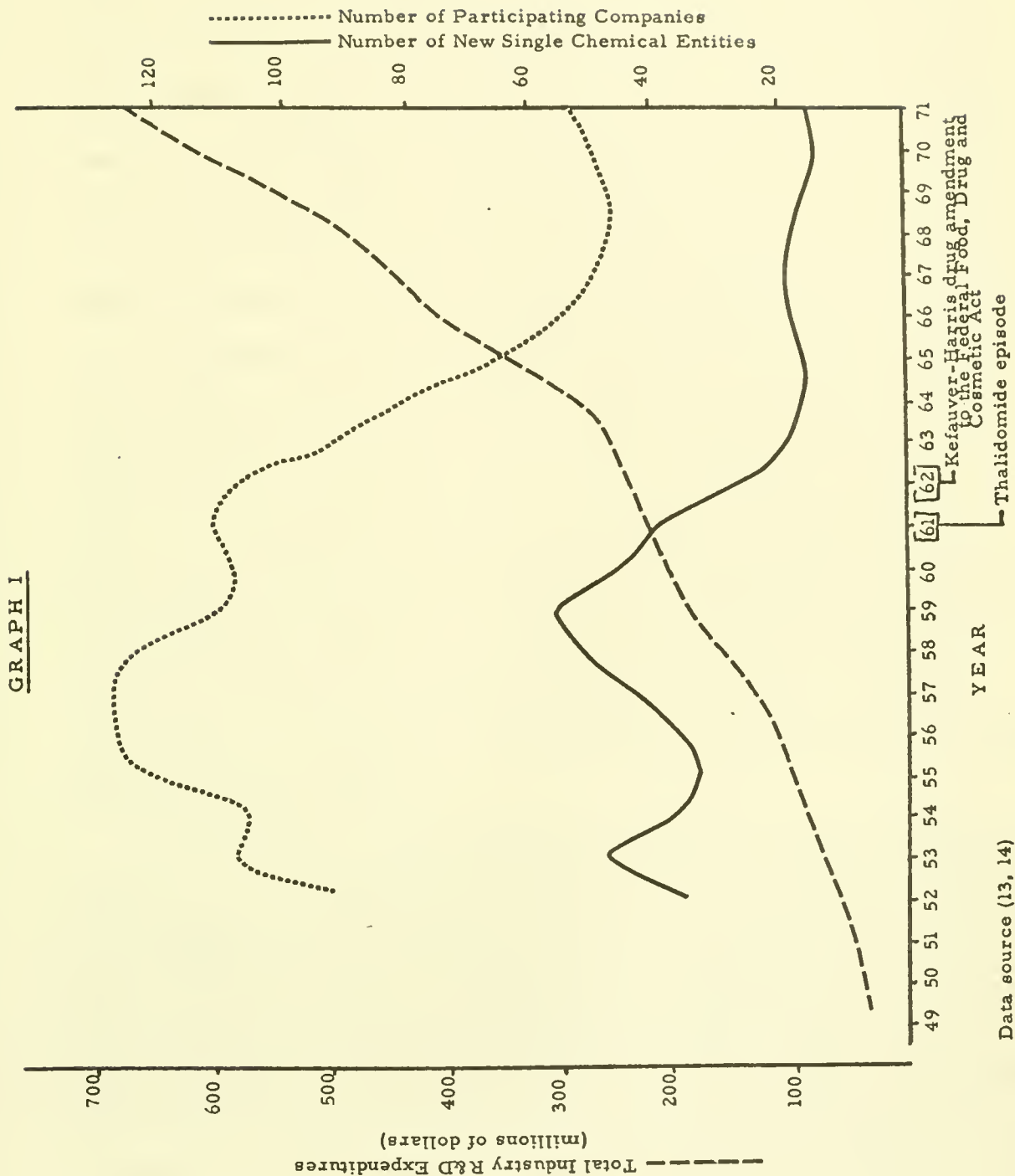
Steady-State System Dynamics of Safety Evaluation R&D in the Pharmaceutical Industry



- I: Studies System Dynamics Model
- II: Petition System Dynamics Model
- III: Consumer Protection System Dynamics Model

These systems dynamics models can be used to describe past extra-organizational interactions involving R&D in the pharmaceutical industry. Using R&D expenditures, number of participating pharmaceutical companies and number of new drugs introduced since 1949, Graph I has been prepared. The data were obtained from sources 13 and 14, and tabulated in Appendix III.

A close inspection of Graph I reveals that the level of the introduction



of new drugs has generally paralleled the number of participating drug companies. In 1961, however, a sharp decrease in the introduction of new drugs occurred a year before a similar decrease in participating drug companies was noted. An explanation for this may be made with the aid of the Consumer Protection Systems Dynamics Model. The initiating event in this case was the thalidomide episode and the resultant Kefauver-Harris Drug Amendment to the Federal Food, Drug and Cosmetic Act. The thalidomide episode triggered sequences 1a and 1b. Since thalidomide-containing drugs had not yet been introduced in the US, they were prevented from commercialization. In light of the deleterious effects initiated by thalidomide, new drugs which contained thalidomide, but had not yet received IND or NDA approvals were delayed by the FDA, pending the development of toxicological methodology designed to determine their mutagenic potential. Subsequently, sequence 2a was initiated, whereby these new toxicological methods were required for all candidate drug chemicals requiring FDA approval. The final outcome of these actions was a decline in the number of participating drug companies until 1965, at which point it levelled off. The stabilization of the introduction of new drugs occurred in 1963.

Simultaneously, R&D expenditures since 1963 have increased considerably. Although the drug companies were becoming more diligent in obtaining IND and NDA approvals, the process was costing them much more. Their reliance on the services of independent contract research laboratories, to the extent of 9.7 million dollars in 1969, indicated that pharmaceutical companies utilized their services in order to offset the increasing costs of their R&D programs. The reliance of two of the independent contract research laboratories on income derived from pre-clinical toxicology, and the attempts of the other two in garnering work in this area, clearly indicates their financial relationship with the phar-

maceutical industry. The Studies System Dynamics Model illustrates this interaction.

As the costs of R&D programs increased following additional R&D requirements instituted by the Kefauver-Harris amendment, fewer pharmaceutical companies elected to participate in new drug development. This resulted in the introduction of fewer new drugs. The data presented in Appendix III show that the 10 year annual average number of participating companies from 1952 to 1961 was 113, while from 1962 to 1971 it declined to 65. A similar decrease in the introduction of new drugs occurred during these same periods. From 1952 to 1961, an average of 43 new drugs were introduced annually. From 1962 to 1971, however, only 18 new drugs were introduced annually. Most interestingly, however, the final result was that the difference between the number of participating drug companies and the number of new drugs introduced annually, was much less from 1962 to 1971, than that seen in the period from 1952 to 1961. The data in Appendix III show the averages of these annual differences. What this indicates, is an increase in the efficiency of the participating pharmaceutical companies in gaining FDA approvals of their new drug applications (NDA's). The Petition System Dynamics Model illustrates the development of this interaction.

Mansfield has reported that R&D management operates in various degrees of uncertainty (12). Research management, according to Mansfield, is characterized by uncertainty, while development management is characterized by less uncertainty. The influence of federal regulatory criteria involving the determination of product safety and efficacy prior to commercialization, interposes another criteria on R&D management not previously reported, that of product compliance management. The action of FDA in approving, or rejecting the IND or NDA petition serves to increase the degree of uncertainty associated with R&D management in the federally regulated pharmaceutical industry. The decision-making

process of the FDA relative to IND's and NDA's results in expanding the time span between the completion of the R&D program and product commercialization. This compliance factor in R&D management is unique to industries whose products are regulated by federal law and administered by federal regulatory agencies.

The emphasis imposed on the management of standardized toxicological methodology was characterized by the employer. The independent contract research laboratory manager was interested in how efficiently he could perform the study and report its results, since income was directly related to his product, the final report. He deals not only with many different pharmaceutical companies, but also companies in other industries whose products are regulated by federal law. The pharmaceutical company manager, on the other hand, was concerned not only with managing his safety evaluation program, but how its results are applied to the IND and NDA petition, and further, the disposition of these petitions by the FDA.

In conclusion, therefore, this working paper identifies the key administrative and economic factors in R&D management associated with the pharmaceutical industry. It develops the verbal theory of cause and effect interaction, and a description of the decision making policies involved with safety evaluation R&D between the pharmaceutical company, the independent contract research laboratory and the FDA. The behavior of negative information feedback systems in R&D management relative to time has been described. Its application to other industries whose products are regulated by federal law based on consumer protection appears highly probable, and the mechanism described in this paper should serve to clarify this complex relationship.

Appendix I

Pharmaceutical Company Questionnaire

1. Name
2. Position
 - a. Education
 - b. Length of employment with the company
 - c. Length of time in present position
 - d. Experience in the company prior to your present position
 - e. Experience prior to joining the company
3. Organizational data of the research facility under your direction
 - a. Laboratory animal toxicology
 1. Professionals
 2. Staff
 3. Facilities
 4. Percent of internal R&D expenditures in this area
 - b. Domestic animal toxicology
 1. Professionals
 2. Staff
 3. Facilities
 4. Percent of internal R&D expenditures in this area
 - c. Analytical chemistry and organic synthesis
 1. Professionals
 2. Staff
 3. Facilities
 4. Percent of internal R&D expenditures in this area
 - d. Industrial hygiene
 1. Professionals
 2. Staff
 3. Facilities
 4. Percent of internal R&D expenditures in this area
 - e. Other
4. What is the product mix of your company?
 - a. Foods
 - b. Food additives
 1. Indirect
 2. Direct
 - c. Drugs
 1. Ethical
 2. Over-the-counter
 - d. Drug devices
 - e. Cosmetics
 - f. Economic poisons

- g. Other
- 5. What is the percent utilization of the laboratory over the past 12 months?
 - a. Total R&D
 - b. Animal toxicology
 - c. Domestic animal toxicology
 - d. Analytical chemistry and organic synthesis
 - e. Industrial hygiene
 - f. Other
- 6. Has your laboratory ever used independent contract research laboratories?
 - a. Yes
 - 1. How frequently?
 - 2. How many?
 - 3. For what type of research?
 - b. No
 - 1. Why?
 - 2. Is this standard operating policy?
- 7. How do the following factors influence your decisions regarding resource allocations relative to the use of independent contract research laboratories?
 - a. Within the company
 - 1. Top management
 - 2. Middle management
 - 3. Current work-load of the laboratory
 - 4. Technical capability of the staff
 - 5. Physical capability of the laboratory
 - 6. Technical feasibility of the project
 - 7. Financial allocation of R&D funds
 - b. Within the independent contract research laboratory
 - 1. Managerial capability
 - 2. Administrative capability
 - 3. Technical capability
 - 4. Location
 - 5. Financial costs
- 8. Do you feel that the use of independent contract research laboratories is advantageous?
 - a. Yes
 - 1. Technically
 - 2. Administratively
 - 3. Financially
 - b. No
 - 1. Why?
- 9. What is your evaluation of independent contract research laboratories?
 - a. Compared to your own laboratory
 - b. Compared to one another

1. Technically
 2. Financially
 3. Administratively
10. On the basis of your experiences, could you comment on whether the use of independent contract research laboratories could, or could not replace any segment of R&D under your direction?
 11. Will your present use of independent contract research laboratories continue as future policy for the company?
 12. What is your evaluation of the Food and Drug Administration?
 - a. Technically
 - b. Administratively (with reference to registration procedures)
 13. What is your evaluation of the Environmental Protection Agency?
 - a. Technically
 - b. Administratively (with reference to registration procedures for economic poisons)
 14. What is the effect of FDA policy on long term R&D management in your company?
 15. Do you anticipate similar FDA-like regulatory activity emanating from EPA and NIOSH to affect your company and industry in the future?
 16. Has your company begun to assemble the internal capabilities to handle regulatory activities originating from these regulatory agencies?
 17. What is your evaluation of your trade organization in its interaction with the FDA?
 - a. As a representative organization of the scientific aspects of your industry
 - b. As a representative organization of the regulatory aspects of your industry
 18. Will internal R&D activity as it is presently constituted in your company continue in the future?
 19. Do you feel that R&D activity in your industry will continue in its present form?

Appendix II

Independent Contract Research Laboratory Questionnaire

1. Name
2. Position
 - a. Length of employment with the firm
 - b. Length of time in present position
 - c. Experience in the firm prior to your present position
 - d. Experience prior to joining the firm
3. Professional activities
 - a. Educational experience
 - b. What professional society memberships do you hold?
 1. Have you attended their annual meetings?
 2. Have you presented papers at these meetings?
 - c. How many trade organization memberships does the firm hold?
 1. Have you attended their annual meetings?
 2. Have you presented papers at these meetings?
 - d. How many publications have you authored?
 1. As a member of the firm
 2. Prior to joining the firm
4. What is the organizational data and history of the firm?
 - a. Is it independently owned?
 - b. Is it a subsidiary?
 1. How long has the firm been a subsidiary?
 2. Have there been management changes within the firm following acquisition?
 - a. Yes
 1. Top management
 2. Project management
 3. Technical staff
 - b. No
 3. Have these changes improved firm performance?
 - a. With private sector clients
 - b. With government contracts
5. What are the products that the firm evaluates?
 - a. Foods
 - b. Food additives
 1. Indirect
 2. Direct
 - c. Drugs
 1. Ethical
 2. Over-the-counter
 - d. Drug devices

- e. Cosmetics
 - f. Economic poisons
 - g. Other
6. How have the services provided by the firm been distributed over the past year?
- a. Laboratory animal toxicology
 - 1. Exploratory
 - 2. Screening
 - 3. Safety
 - 4. Efficacy
 - 5. Metabolism
 - 6. Other
 - b. Domestic animal toxicology
 - 1. Exploratory
 - 2. Screening
 - 3. Safety
 - 4. Efficacy
 - 5. Metabolism
 - 6. Other
 - c. Analytical chemistry
 - 1. Food additives
 - 2. Drugs
 - 3. Economic poisons
 - 4. Other
 - d. Clinical chemistry
 - e. Industrial hygiene
 - 1. Environmental exposure
 - a. Air pollution
 - b. Water pollution
 - 2. Occupational exposure
 - f. Other
7. Has the use of services provided by the firm for the past year typified previous yearly trends?
- a. Yes
 - b. No
 - c. Has there been any reason behind a shift to the present distribution of services?
 - 1. Internal
 - a. Development of new methods
 - b. Procurement of new personnel
 - 2. External
 - a. New ventures taken by your clients
 - b. Regulatory activities dictating a change
8. How do the following factors influence your decisions regarding resource

allocations?

- a. Top management
 1. Within the firm if independently owned
 2. Within the parent organization if a subsidiary
 - b. Technical feasibility of the project
 - c. Technical capability of the laboratory and staff
 - d. Financial allocation of funds
 - e. Regulatory climate
 - f. Current work-load of the laboratory
 - g. Current status of the business viability of the firm
9. How do the following factors affect your decision-making activities?
- a. Expanding an existing service
 - b. Decreasing an existing service
 - c. Eliminating an existing service
 - d. Initiating a new service
10. How do the following factors influence the project proposals initiated by the firm?
- a. Existence of a need for technical services offered by the firm
 - b. Technical expertise of the professional staff
 - c. Technical feasibility of the project
 - d. Viability of the commitment of the project to the firm
11. What is the level of professional staff effort involved with governmental client contact?
- a. What is the total number of professionals involved?
 - b. Has this number increased, decreased or remained constant over the past year?
12. What is the level of professional staff effort involved with private sector client contact?
- a. What is the total number of professionals involved?
 - b. Has this number increased, decreased or remained constant over the past year?
13. Once a contract has been received, what has been the level of client contact during the period of the study?
- a. Sequence
 1. Before receiving the request for proposal (RFP)
 2. Before receiving the contract
 3. During the study period
 4. Following the issuance of the final report
 5. Average during acute studies
 6. Average during subacute studies
 7. Average during chronic studies
 - b. Has client contact shifted from one level of professional to another following the receipt of the contract?

1. Within the laboratory
 2. Within the client's laboratory
14. Can any correlation be made as to the technical, or managerial level of the professional involved in client contact relative to the number of contracts?
 15. Are your client contacts technical or administrative personnel?
 16. Does your client contact policy change as to whether they are technically or administratively oriented?
 17. On the basis of your experiences, do you feel that clients with technical backgrounds utilize your services more effectively than clients with administrative backgrounds?
 18. Have you been able to determine if there is a positive correlation between client contact and client satisfaction?
 19. Do you perform the following evaluation procedures involving the service that the firm provides?
 - a. Administrative survey
 1. Date the sample was received
 2. Date the initiation of the study
 3. Date the termination of the study
 4. Date the issuance of the final report
 - b. Technical survey
 1. Do you monitor the following items regarding the conduct of the study?
 - a. Errors of omission
 - b. Errors of commission
 2. Do you monitor the following items regarding the final reports?
 - a. Errors of omission
 - b. Errors of commission
 20. How often do you review your internal evaluation procedures?
 - a. Once a month
 - b. Once every other month
 - c. Once every quarter
 - d. Once every other quarter
 - e. Once a year
 - f. For all client accounts?
 - g. Prior to client contacts?
 21. Have these procedures aided your management of the firm?
 22. Have these quality control procedures improved the services offered to your clients?
 23. What are the procedures used in evaluating the firm's technical and

financial performances?

a. Internally

1. Total number of clients
2. Amount of repeat business
3. Total amount of contract work
4. Cash flow
5. Number of staff over a fixed period of time
6. Size of the facility over a fixed period of time

b. Externally

1. Performance in competitive bidding on identical projects
2. Performance in services offered in areas serviced by competitors
3. Client feed-back on the firm's performance
4. Market survey of competitors

c. What was the profit picture of the firm for the past 5 years?

d. What were the primary factors, in your opinion, responsible for this performance?

1. Billings
2. Direct costs
3. Indirect costs

24. What is your evaluation of independent contract research laboratories?

- a. Relative to the firm
- b. Relative to each other

25. What is your evaluation of industrial research laboratories?

- a. In toxicological research
- b. In areas similar to what your firm offers in services
- c. Clients with large research facilities
- d. Clients with medium research facilities
- e. Clients with small research facilities

26. What is your evaluation of the regulatory agencies?

- a. Food and Drug Administration
 1. Technical
 2. Administrative (registration)
- b. Environmental Protection Agency
 1. Technical
 2. Administrative (registration)

27. What have been the primary factors responsible for the success of the firm?

28. On the basis of your experiences, could you comment on whether the use of independent contract research laboratories could, or could not replace R&D capabilities in:

- a. Industrial research laboratories
- b. Governmental research laboratories

29. Have you been able to observe any trends in the business of independent contract research laboratories over the past year?

Appendix III *

<u>Year</u>	<u>Total Industry R&D Expendi- tures. (million \$)</u>	<u>Number of New Single Chemi- cal Entities Introduced</u>	<u>Number of Participating Companies Surveyed</u>	<u>Difference be- tween Companies and New Single Chemical Entities</u>
1949	34	--	--	--
1950	39	--	--	--
1951	50	--	--	--
1952	63	35	89	54
1953	67	48	107	59
1954	78	38	101	63
1955	91	31	124	93
1956	105	42	126	84
1957	127	51	127	76
1958	170	44	126	82
1959	197	63	106	43
1960	206	45	109	64
1961	227	41	111	70
average; <u>1952-1961</u>	---	<u>43</u>	<u>113</u>	<u>70</u>
1962	244 [#]	28	108	80
1963	269 [#]	18	89	71
1964	298	17	82	65
1965	357	23	65	42
1966	402	13	52	39
1967	448	25	49	24
1968	485	14	48	34
1969	549	11	48	37
1970	619	16	60	54
1971	681	14	46	32
average; <u>1962-1971</u>	---	<u>18</u>	<u>65</u>	<u>57</u>

* Data derived from sources 13, and 14

Averaged between both sources

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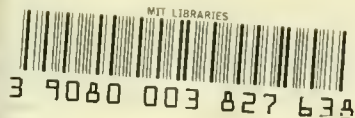
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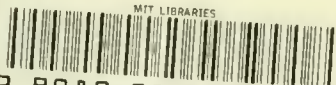
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